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RESEARCH**

APPLICATION NUMBER:

205776Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 6, 2014
From	Janet Maynard, MD, MHS
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	205776
Supplement#	
Applicant	Medac Pharma, Inc
Date of Submission	September 10, 2013
PDUFA Goal Date	July 10, 2014
Proprietary Name / Established (USAN) names	Rasuvo/methotrexate injection
Dosage forms / Strength	7.5mg/0.15mL autoinjector, 10mg/0.20mL autoinjector, 12.5mg/0.25mL autoinjector, 15mg/0.30mL autoinjector, 17.5mg/0.35mL autoinjector, 20mg/0.40mL autoinjector, 22.5mg/0.45mL autoinjector, 25mg/0.50mL autoinjector, 27.5mg/0.55mL autoinjector, 30mg/0.6mL autoinjector
Proposed Indication(s)	1. Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis 2. Severe Psoriasis
Recommended:	<i>Approval, pending inspection findings</i>

1. Introduction

This is a 505(b)(2) new drug application (NDA) for a drug/device combination product (trade name: Rasuvo) consisting of an injectable methotrexate (MTX) formulation in a single-use prefilled autoinjector intended for subcutaneous administration only. Ten strengths are proposed: 7.5mg, 10mg, 12.5mg, 15mg, 17.5mg, 20mg, 22.5mg, 25mg, 27.5mg, and 30mg. Each dose is obtained by keeping a fixed methotrexate concentration (50mg/mL) and varying the volume of fill in the device. The device is a single-use, single-dose, prefilled, manually-triggered, pen autoinjector.

Methotrexate tablets have been marketed since December of 1953 (NDA 08085, Dava Pharmaceuticals Inc.) when the product was approved for the treatment of acute leukemia in adults. In addition to tablets, methotrexate is approved as an injection (NDA 11719; approved 1959; Hospira) for intramuscular (IM), intravenous (IV), subcutaneous (SC), intra-arterial (IA), and intra-theal (IT) administration. Methotrexate is currently available in 2.5 mg tablets (multiple companies), and 5, 7.5, 10, and 15 mg tablets (Barr). Injectable methotrexate is available from multiple companies in varying quantities of 25 mg/mL solution. At the time of submission of this NDA, approved indications and routes of administration for methotrexate included neoplastic diseases (oral, intramuscular, intravenous, intra-articular, and intra-theal routes), rheumatoid arthritis (oral route), polyarticular course juvenile rheumatoid arthritis

(oral, intramuscular, subcutaneous routes), and severe psoriasis (oral, intramuscular, intravenous routes). Of note, polyarticular juvenile rheumatoid arthritis (JRA) is now called polyarticular juvenile idiopathic arthritis (pJIA). On October 14, 2013 (after submission of this NDA), a methotrexate autoinjector (Otrexup, NDA 204824, Antares Pharma, Inc.) was approved for the treatment of rheumatoid arthritis, pJIA, and severe psoriasis. Otrexup is a single-use, single-dose, prefilled, autoinjector intended for subcutaneous administration only.

In this NDA, the Applicant is seeking approval of their product and the subcutaneous (SC) route of administration for the rheumatoid arthritis (RA) and psoriasis indications, as well as the polyarticular juvenile arthritis indication which is already approved for SC administration in other parenteral methotrexate labels. To support the new route and indication, the Applicant is relying on:

- The Agency's previous findings of safety and effectiveness of methotrexate in adults with RA (oral route) and psoriasis (oral, IM, and IV routes), and in children with JRA (oral, SC, and IM routes)
- Information in the published literature supporting the safety and efficacy of subcutaneously administered methotrexate for RA, pJIA, and psoriasis
- A relative bioavailability (BA) study (MC-MTX.14/PK) in healthy adults that showed equal or greater bioavailability of methotrexate SC administered via the Applicant's autoinjector compared to the exposure obtained with orally administered methotrexate tablets.

The primary data to support this NDA submission and approval for all of the proposed indications are from the BA study comparing the proposed SC methotrexate product to oral methotrexate (MC-MTX.14/PK). The Applicant also performed a BE study (MC-MTX.12/PK) comparing the proposed product administered SC to the reference parenteral drug Hospira administered IM. The results of the study became available during the course of the review. While not required to support approval, these results were reviewed.

To support approval of the autoinjector device, the Applicant also performed an actual use study (MC-MTX.15/HF) to demonstrate that patients and caregivers could be taught to successfully administer the product.

The Applicant proposed labeling that was consistent with the approved listed drugs for the indications of psoriasis, pJIA, and RA. Thus, a collaborative review was conducted with review of the RA and pJIA indications in the Division of Pulmonary Allergy, and Rheumatology Products (DPARP) and review of the psoriasis indication in the Division of Dermatology and Dental Products (DDDP). This review discusses the three indications proposed in the application.

2. Background

Methotrexate history

In the 1940's, folic acid antagonists were first postulated as potential treatment for leukemias, with the first successful drug being the folate analog aminopterin, demonstrated by Sidney Farber in 1947 to induce remission in children with acute lymphocytic leukemia. Other folate analogs, such as methotrexate, soon followed in the 1950's. Due to methotrexate's improved tolerability and easier production, it became the preferred treatment for a number of malignancies and neoplasms.

Although aminopterin was investigated as a treatment for RA as early as 1951, and methotrexate as early as 1962, use of methotrexate for RA languished until the 1970's and 1980's. The reason for this disinterest is not known, but is postulated by some to be due to a greater enthusiasm for corticosteroids during that time frame. Throughout the 1980's interest in methotrexate blossomed, prompting an increasing number of clinical studies and controlled trials of methotrexate, and culminating in the FDA approval of methotrexate for RA in 1988¹. Although the pivotal trials for the approval of methotrexate evaluated oral methotrexate, the gastrointestinal tolerability issues, relatively poor oral absorption of methotrexate at higher doses, and ready availability of parenteral methotrexate quickly led practitioners to use parenteral methotrexate as an alternative for patients who were not tolerating oral methotrexate². However, the labels of currently approved methotrexate products only specifically mention the subcutaneous route of administration for polyarticular-course juvenile rheumatoid arthritis (now called polyarticular juvenile idiopathic arthritis or pJIA) indication, and only oral dosing is mentioned for RA.

Regulatory history

The Agency had multiple pre-submission interactions with Medac between 2010 and 2012, including meetings with DPARP and DDDP to discuss the requirements for an NDA submission (pre-IND [DPARP]: 10/14/10, additional pre-IND questions [DPARP]: 12/27/11 (written responses), pre-IND [DDDP]: 2/22/12, initial pediatric study plan submission [DPARP]: 12/2/12, and pre-NDA [DPARP and DDDP]: 6/17/03).

At the pre-IND meeting with DPARP (IND 109543) on October 14, 2010, the Applicant proposed pursuing a 505(b)(2) application using methotrexate solution as the reference listed drug. It was noted that methotrexate solution for injection is only approved for psoriasis, pJIA, and oncology indications. The injectable methotrexate label references the oral formulation for the treatment of RA, but does not include efficacy, safety, or dosing information for injectable methotrexate for this indication. Thus, DPARP suggested that the Applicant consider the psoriasis indication as well. The Applicant was told that data would be needed to support SC dosing for an RA indication, although the data might be available in published literature.

¹ Cury FF and Weinblatt ME, Clin Exp Rheumatol 2010;28(Suppl 61):S9-S12.

² Visser et al, Ann Rheum Dis 2009 Jul;68(7)1086-93.

The Applicant submitted additional pIND questions to DPARP on October 31, 2011, and written responses were sent on December 27, 2011. At that time, the Applicant proposed a meta-analysis of all data regarding methotrexate in RA, an efficacy study evaluating the safety and efficacy of methotrexate administered SC, and a PK study of methotrexate administered SC with the proposed autoinjector compared to oral administration of the listed drug. DPARP noted that an efficacy study might not be necessary as evidence to support their planned 505(b)(2) application could come from published literature. The Applicant was told that to support approval of a methotrexate autoinjector for the indication of RA, the Applicant would need a bioavailability study comparing the proposed SC route of administration to the approved oral route of administration and an actual use study in RA patients.

At the pre-IND meeting with DDDP (IND 113735) on February 22, 2012 the Division recommended a relative BA study comparing SC with IM methotrexate administered at the highest recommended dose of 30mg in psoriasis patients.

On December 2, 2012, the Applicant submitted an initial pediatric study plan. The FDA provided written comments on this plan on March 6, 2013. It was noted that the safety and efficacy of methotrexate for children with JIA has been established based on the proposed listed drug's label and the available scientific literature.

At the pre-NDA meeting on June 17, 2013 with DDDP and DPARP, it was noted it would be reasonable to perform a relative bioavailability study comparing oral methotrexate to SC methotrexate for all of the proposed indications. Further, at the pre-NDA meeting the summary of the development plan in support of a 505(b)(2) NDA submission for methotrexate was consistent with the advice provided by the Divisions during previous interactions. Therefore, it was felt that the program was generally acceptable to support submission of the Applicant's application. Expectations regarding the NDA content and format were also discussed.

3. CMC/Device

*Primary CMC reviewer: Arthur B. Shaw, Ph.D.; CMC Supervisor: Craig Bertha, Ph.D.
CDRH General Hospital Devices Branch: Keith Marin, MS, MBA, OCN
Product Quality Microbiology Reviewer: Robert J. Mello, Ph.D.*

- **General product quality considerations**

Drug substance

Methotrexate is a yellow to orange, crystalline powder, insoluble in water. The CMC information for methotrexate is covered in DMF (b) (4) which has been reviewed many times and has been found acceptable. A recent amendment contains a number of changes in the manufacturing which have been reviewed and found acceptable. The specifications and testing for the drug substance are provided in the NDA, both in terms of Certificates of

Analysis (COAs) from the supplier and in terms of complete testing by the manufacturer of the drug product. The testing conforms to both the United States Pharmacopeia (USP) and the European Pharmacopeia (Ph.Eur.). All process-related impurities are well-controlled and degradation is minimal. The major degradant, (b) (4) and has no additional toxicity. The Applicant has proposed a reduced testing program for release of the drug substance by the drug product manufacturer after the first commercial batches. The CMC review team has determined this to be acceptable.

Drug product

The drug product is formulated by (b) (4). No preservatives are added, since the drug product is intended for single use in a custom injector. The drug product solution is (b) (4) into glass syringes and closed with a plunger with a rubber stopper. The safety of leachables that have been observed from the packaging components in direct contact with the drug product was evaluated by the Pharm/Tox staff and found to be acceptable. The preparation, including sterilization, of the syringes and the plunger are covered in DMFs which have been reviewed by the product quality microbiology reviewer, Dr. Mello, and found to be acceptable. The sterility aspects of the drug product manufacturing have been reviewed by Dr. Mello and found to be acceptable.

The drug is formulated at one strength (50 mg/mL) to be delivered at 10 different volumes to achieve different strengths to be delivered to the patients (7.5 mg/0.15 mL methotrexate, 10 mg/0.20 mL methotrexate, 12.5 mg/0.25 mL methotrexate, 15 mg/0.30 mL methotrexate, 17.5 mg/0.35 mL methotrexate, 20 mg/0.40 mL methotrexate, 22.5 mg/0.45 mL methotrexate, 25 mg/0.50 mL methotrexate, 27.5 mg/0.55 mL methotrexate, 30 mg/0.60 mL methotrexate). The drug product specifications are adequate to support release of the drug. An unidentified impurity at RRT=(b) (4) min increases steadily at (b) (4) reported in the application. The Agency's statistical analysis shows that the upper 95% confidence limit for this impurity exceeds the acceptance criteria of (b) (4) at 17 months. This will be the recommended expiration date.

The primary container closure for drug product is the (b) (4) 1mL long syringe made of Type I (b) (4) glass barrel, embedded with 27 gauge, ½ inch stainless steel needle, needle shield and (b) (4) rubber plunger stopper.

Device

The pre-filled syringes (PFS) are loaded manually into a custom device, covered by a device master file (MAF (b) (4)). The syringe inside the device is the to-be-marketed product, a drug-device combination. The device is designed to deliver a fixed volume with no measuring by the patient. The needle is completely covered when not in use both before and after activation of the device so that the chances of accidental injection or exposure to the needle are minimized. When the device is activated the force of delivery is controlled by a spring in the device, not the patient. The average injection delivery time for the 30mg dosage strength is approximately 2.5 seconds. The needle is an appropriate length (exposed needle length

8mm±2mm) to ensure that the drug is administered subcutaneously. After the device is actuated there is no drug remaining in the syringe so that safe disposal is not an issue. The device performance was found acceptable by the CDRH reviewer, Keith Marin.

During review of the device testing, CDRH noted that the Applicant performed testing with an older standard (ISO 11608-1:2000). The Applicant was asked to compare the ISO 11608-1:2000 version of the standard to the more recent ISO 11608-1:2012 version and to perform tests that have different requirements or additional new testing for each dosage volume. The Applicant provided a comparison of the standards. The CDRH device reviewer felt that this comparison and the other testing performed by the Applicant, such as simulated shipping studies, were sufficient. In addition, the CDRH device reviewer determined that a bracketed approach that tested the highest and lowest dose would be acceptable for dose accuracy because the device utilizes differences in fill volume for different doses. Thus, additional device testing is not required and the data submitted are adequate to support the device according to Keith Marin the CDRH device reviewer.

An actual use study (Study MC-MTX.15/HF) was performed to evaluate the ability of patients to follow the instructions for use and use the device. This study is described in further detail in Section 8 below.

- **Facilities review/inspection**

The drug substance is manufactured at [REDACTED] (b) (4) which has a satisfactory cGMP status as of 09/30/2013.

Microbiology testing and residual solvent testing is performed by [REDACTED] (b) (4) which has acceptable status as of 11/22/2013.

Visual inspection of pre-filled syringes, testing of primary packaging materials, testing of excipients except physico-chemical testing of water for injection, and assembly, labeling, packing, storing, and release testing is performed at [REDACTED] (b) (4). Evaluation of this site is pending at the time of this review.

Manufacture of the 50mg/mL solution pre-filled syringes, [REDACTED] (b) (4) is performed at Oncotec Pharma Produktion GmbH, Am Pharmapark 06861, Dessau-Roßlau, Germany, which was inspected April 10-17, 2014. The results of the inspection are pending at the time of this review.

- **Other notable issues (resolved or outstanding)**

The CMC review team has concluded that the application may be approved from a CMC perspective.

4. Nonclinical Pharmacology/Toxicology

Primary reviewer: Jane Sohn, Ph.D.; Team Leader: Timothy Robison, Ph.D.

- **General nonclinical pharmacology/toxicology considerations**

The pharmacologic and toxicologic properties of methotrexate are well known from the 60 years of clinical use in humans. The systemic safety of methotrexate is supported by reference to approved methotrexate products. The Applicant submitted a single dose local tolerance study. In addition, the Applicant submitted an assessment of leachables and extractables, which includes evaluation of [REDACTED] (b) (4)

[REDACTED] The data were reviewed by Dr. Sohn and determined to be acceptable.

- **Other notable issues (resolved or outstanding)**

The Applicant submitted a single dose GLP rabbit study. The animals received single doses of 25mg methotrexate (50mg/ml) on their left side and single doses of 0.9% aqueous sodium chloride solution on their right side. Animals were dosed by intravenous, intraarterial, intramuscular, paravenous, and subcutaneous bolus injection. At 48 hours, 96 hours, and 14 days after administration, 2 animals were sacrificed and the injection sites were examined. There were no test article related findings.

The pharmacology/toxicology team has concluded that as the safety profile of methotrexate is well-established based on clinical experience by multiple routes of administration, including the subcutaneous route and the data submitted are adequate to support approval of the NDA from the nonclinical perspective.

5. Clinical Pharmacology/Biopharmaceutics

Primary clinical pharmacology reviewers: Sheetal Agarwal, Ph.D. and Doanh Tran, R.Ph., Ph.D.; Clinical pharmacology team leaders: Satjit Brar, Pharm.D., Ph.D. and Hae Young Ahn, Ph.D.

- **General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.**

This NDA references two previously approved methotrexate products: NDA 11719 (Hospira's methotrexate injection, the reference listed drug for parenteral methotrexate products) and NDA 8085 (Dava's oral methotrexate tablets, the reference listed drug for oral methotrexate products).

Study MC-MTX.14/PK evaluated the PK of Medac's methotrexate autoinjector (trade name Rasuvo) compared to methotrexate oral tablets. The intent of this study was to allow for bridging to approved RA and psoriasis doses and inform SC dosing. Results indicated that methotrexate exposure ($AUC_{(0-inf)}$) was higher with the Rasuvo methotrexate autoinjector

compared to oral methotrexate at all dose levels tested (7.5, 15, 22.5, and 30mg). However, the quantitative difference in systemic exposure was not the same across the doses, and ranged between 33% higher (at the 7.5mg dose) to 66% higher (at the 30mg dose). This is consistent with the known properties of orally administered methotrexate; oral bioavailability decreases at high doses, likely due to a saturable intestinal active transport absorption mechanism with low capacity characteristics.³ The differences in bioavailability of methotrexate with Rasuvo compared to oral methotrexate tablets will be included in the label.

Study MC-MTX.15/HF evaluated effect of body weight (60-100kg vs. less than 60kg and higher than 100kg) and effect of injection site (abdomen vs. upper thigh) on systemic exposure of methotrexate when administered SC by the Rasuvo autoinjector. The PK evaluation was conducted in a subset of 24 patients (out of 104 patients) only. The PK data showed that in subjects weighing more than 100kg, mean AUC and mean C_{max} of methotrexate decreased by approximately 16% and 33% respectively as compared to the 60-100kg group. In addition, the study showed that while absorption of methotrexate was higher through abdomen vs. thigh in subjects weighing less than 100kg, absorption of methotrexate was higher through thigh vs. abdomen in subjects weighing more than 100kg. As the number of subjects in each of these categories was too small to make a meaningful conclusion, and since methotrexate is generally titrated to a therapeutic dose, the differences in methotrexate absorption across subjects of different weights or through different injection sites are not considered clinically relevant and will not be included in the labeling.

Study MC-MTX.12/PK evaluated the PK of Medac's methotrexate autoinjector compared to methotrexate injection administered by needle and syringe. This study was not required for submission or filing of this NDA as the primary data to support approval of the subcutaneous route of administration of methotrexate for RA and psoriasis is based on the relative BA study comparing the PK of Medac's methotrexate autoinjector to methotrexate oral tablets. The results of this study became available during this NDA review. The results were reviewed, but were not required to support approval of this application. Methotrexate exposure (AUC values) for methotrexate administered IM was comparable to the exposure from Medac's methotrexate autoinjector at the same dose.

Other relative bioavailability studies of SC methotrexate in the literature

Jundt et al. 1993.⁴ This study evaluated the relative bioavailability of low dose methotrexate administered as tablet, oral solution, and SC injection to that of IM injection in patients with rheumatoid arthritis (RA). Twelve patients meeting the American College of Rheumatology criteria for RA had serial blood methotrexate concentration samples drawn over a 24-hour period after receiving their normal weekly methotrexate dose. Relative bioavailability of the tablet and oral solution formulations was determined by comparison of the AUC for the 2 different oral formulations as a percentage of the AUC for IM injection. Also, relative bioavailability of the SC formulation was compared to IM in 6 of the patients. Results showed that bioavailability of the oral solution and oral tablet were similar, but approximately 15

³ Abolmaili et al., Cancer Chemother Pharmacol, 2013, 71:1115-1130.

⁴ Jundt JW et al., J Rheumatol 1993 Nov; 20(11):1845-9.

percent less than the IM. The relative bioavailability of methotrexate via SC and IM routes was similar.

Hoekstra et al. 2004.⁵ This study evaluated the bioavailability of higher oral doses of methotrexate compared to SC methotrexate in adult patients with RA. A pharmacokinetic analysis was performed in 15 patients with RA taking a stable dose of methotrexate (> or = 25 mg weekly). Separated by 2 weeks, a pharmacokinetic analysis was performed in each patient after oral and subcutaneous administration of the same dose of methotrexate. The median methotrexate dose was 30 mg weekly (range 25-40 mg). The mean bioavailability after oral methotrexate was 0.64 (range 0.21-0.96) compared to subcutaneous administration (i.e. SC administration resulted in 26% higher exposure). There was a statistically significant difference in the bioavailability of the two administration regimens.

Thus study MC-MTX.14/PK results were consistent with the oral/SC relative bioavailability of methotrexate reported in the published literature.

- **Other notable issues (resolved or outstanding)**

An OSI inspection request was made for the relative BA study MC-MTX.14/PK. As noted in Section 11 of this review, the results from the clinical and bioanalytical portions of study MC-MTX.14/PK were felt to be acceptable for Agency review.

The clinical pharmacology team finds the NDA acceptable for approval from a clinical pharmacology perspective.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Primary clinical reviewers: Peter Starke, M.D. (DPARP), Denise Cook, M.D. (DDDP)

As discussed in Section 5, compared to oral methotrexate tablets, the exposure (AUC) of methotrexate given subcutaneously via the Medac methotrexate autoinjector was approximately 33 to 66% higher, depending on the dose. Therefore, the efficacy of SC methotrexate could be presumed based on exposures that are equal or greater than exposures via the approved oral route of administration. This is also based on the assumption that clinically significant immunogenicity is unlikely with the change in route of administration, since this is a small molecule chemical.

In addition to this pharmacokinetic (PK) bridge, the Applicant summarized the clinical efficacy and safety data on SC methotrexate from the literature, as requested by the Agency.

⁵ Hoekstra M et al., J Rheumatol 2004 Apr; 31(4):645-8.

In addition, Dr. Starke, Dr. Cook, and I conducted a review of the available literature for SC methotrexate treatment. This literature includes a randomized controlled trials (Braun 2008) and multiple studies and clinical reports. Some highlights of the literature review are summarized in here:

Braun et al, 2008.⁶ The Applicant submitted the study report for this published study. This was a 6-month randomized, double-dummy, controlled trial in 384 methotrexate-naïve RA patients who were randomized 1:1 to either 15mg of SC methotrexate + placebo oral tabs or 15mg of oral methotrexate + placebo SC injection. Injections were administered via prefilled syringe. At Week 16, patients who did not meet ACR criteria for 20% improvement (ACR20) were switched from 15mg orally to 15mg SC or from 15mg SC to 20mg SC, and continued the remaining 8 weeks in a blinded fashion. These patients were counted as nonresponders for the Week 24 endpoint. Results were as follows:

Table 1: SC vs. oral methotrexate, ACR Responses at Week 24

	ACR20	ACR50	ACR70
SC Methotrexate	78%*	62%	41%*
Oral Methotrexate	70%	59%	33%

*difference vs. oral p<0.05

Similar results were observed for the components of the ACR response criteria, such as number of swollen joints and number of tender joints, and Health Assessment Questionnaire Disability Index (HAQ-DI), as well as for another composite efficacy measure, the Disease Activity Score (DAS)-28. At Week 16, 30 patients were switched from 15mg orally to 15mg SC with an additional 30% of them achieving an ACR20 response at Week 24. Twenty-two patients were switched from 15mg to 20mg with an additional 23% of them achieving an ACR20 at Week 24.

Other supportive studies in RA

Parker et al. 2004.⁷ This prospective, randomized crossover trial assessed the clinical utility of increasing the methotrexate dose from 20 mg/week to 25 mg/week either orally or SC in 8 RA patients (5 females) with active RA refractory to their current DMARD regimen. After ≥8 weeks of oral methotrexate at a dose of 20 mg/week, eligible patients were randomly assigned to receive 25 mg/week administered either SC or orally for 8 weeks and then crossed over to the alternate route for an additional 8 weeks. Patients were evaluated by blinded assessors using the modified HAQ, patient's global assessment, physician's global assessment, joint counts, and ESR. Two patients had a significant response when methotrexate was administered SC. One of these patients showed no improvement after 8 weeks of oral methotrexate at 25 mg/week, but achieved an ACR20 improvement when crossed over to SC methotrexate. The other patient achieved an ACR50 while on SC methotrexate, but returned to her active baseline level when crossed over to oral methotrexate. Following completion of the study, the patient switched back to SC methotrexate and achieved an ACR50 again. The

⁶ Braun J et al., Arthritis Rheum 2008;58(1):73-81.

⁷ Parker CT et al., J Am Osteopath Assoc. 2004; 104(1):7-8.

authors concluded that some patients with active RA who are taking 20 mg/wk or oral methotrexate may respond to 25 mg/wk if the route of administration is changed to SC injection.

Thornton et al. 2008.⁸ This was a prospective study to investigate the effectiveness of SC methotrexate in a cohort of patients for whom oral methotrexate was ineffective or not tolerated. Thirty patients were enrolled and assessed at 3 and 6 months after switching to SC methotrexate. Based on European League Against Rheumatism (EULAR) response criteria, 20/27 (74%) of patients had a good response at 3 months and 13/25 (52%) had a good response at 6 months.

Bakker et al. 2010.⁹ As part of a 2-year prospective, randomized, open-label multi-center trial in Netherlands comparing two methotrexate regimens intended to evaluate the benefit of “tight control” of RA patients, 57/151 patients were switched from oral to SC methotrexate (21 due to adverse effects on a mean oral dose of 25 mg/week, and 36 due to lack of efficacy at a maximum dose of 30 mg/week). After switching to SC methotrexate, 36 patients experienced additional improvement by 1 and 4 months post switch and 21 did not.

The Applicant submitted many articles describing the efficacy of methotrexate in different groups of RA patients. These articles support the efficacy of methotrexate appears similar, regardless of the route of administration. These additional articles are described in detail in Dr. Starke’s clinical review.

Supportive data in severe, disabling psoriasis

The Applicant summarized the literature supporting subcutaneous methotrexate administration in severe, disabling psoriasis. These are also described in Dr. Cook’s review. The primary support was from two articles (Inzinger 2013 and Yesudian 2012).

Inzinger 2013.¹⁰ This was a patient registry in which patients with moderate-to-severe chronic plaque psoriasis were treated with methotrexate (n=71) or fumaric acid esters (n=200). Methotrexate was administered SC (n=48) and orally (n=24). Among the patients who completed at least 3 months of treatment, the primary treatment response with methotrexate and fumaric acid esters did not differ significantly at any time point. There were no statistically significant differences in efficacy results for the oral compared to the SC methotrexate groups. The authors concluded that the primary efficacy of fumaric acid esters and methotrexate (either oral or SC) was similar.

Yesudian 2012.¹¹ This article was a case series that describes 36 patients with chronic plaque psoriasis who had all previously tried oral methotrexate and then switched to SC methotrexate for a variety of reasons. Of the 36 patients, 25 were classified as responders and 11 were

⁸ Thornton C et al. Rheumatology (Oxford). 2008; 47(9):1438.

⁹ Bakker MF et al. Ann Rheum Dis. 2010; 69(10):1849-52.

¹⁰ Inzinger M, et al 2013. JEADV 27, 861-866.

¹¹ Yesudian et al, 2012. British J Derm 2012;167(Suppl. 1), 21-69.

classified as non-responders to SC methotrexate. The authors concluded that SC methotrexate is an option for patients with chronic plaque psoriasis.

The Applicant submitted articles and treatment guidelines to support the efficacy of methotrexate in different groups of psoriasis patients. These articles support the efficacy of methotrexate for psoriasis. While there are limitations to these studies, they provide supportive data regarding the efficacy of methotrexate for severe psoriasis. See Dr. Cook's review for additional details.

Supportive data in JIA

The Applicant also summarized the literature supporting subcutaneous methotrexate administration in children with juvenile idiopathic arthritis (JIA). These are also described in Dr. Starke's review. However, as the approved methotrexate labels already note subcutaneous administration as an available route of administration for JIA, evidence to support the efficacy of this route of administration in JIA is not necessary and will not be described here.

- **Notable efficacy issues both resolved and outstanding**

Given that the SC route of administration results in 33 to 66% higher exposure compared to orally administered methotrexate, the efficacy of SC methotrexate may reasonably be extrapolated from the evidence supporting the efficacy of orally administered methotrexate for RA and severe, disabling psoriasis. This conclusion is supported by the randomized controlled study by Braun et al (which showed that SC methotrexate at the same dose resulted in a similar or higher proportion of ACR responders compared to oral methotrexate), and other published literature in RA and psoriasis. Dr. Starke, Dr. Cook, and I are in agreement that there is adequate evidence to support the efficacy of the subcutaneous route of administration of methotrexate in RA and severe, disabling psoriasis.

8. Safety

- **Discuss the adequacy of the database, major findings/signals, special studies, etc.**

The ranges of doses currently approved for methotrexate are summarized in Table 1 below.

Table 1: Approved Doses of Methotrexate

Indication	Dose Regimen
Trophoblastic diseases	15 to 30 mg daily oral or intramuscularly (IM) x 5 days; repeat as needed after rest period
Leukemia	Induction: 3.3 mg/m ² (6 to 7 mg for avg. US adult ¹²) daily until remission Maintenance: 30 mg/m ² (54 to 61 mg for avg. adult) two times/week oral or IM or 2.5 mg/kg (187 to 217 mg for avg. adult) intravenously (IV) every 14 days
Lymphoma	Burkitt's Stage I-II: 10 to 25 mg/day orally for 4 to 8 days; repeat as needed after rest period; Stage III: with other therapy: 0.625 to 2.5 mg/kg daily (~47 to 217 mg)
Mycosis fungoides	5 to 50 mg once weekly or 15 to 37.5 mg twice weekly
Osteosarcoma	12 to 15 <u>grams</u> /m ² (~21 to 31 <u>grams</u> for avg. US adult) IV, to achieve serum concentration of 1000 μM, with leucovorin rescue
Psoriasis	10 to 25 mg/week oral, IM or IV, adjust to response, >30 mg/week not recommended
Adult RA	Only starting dose is specified: 7.5 mg orally once weekly in single or divided dose, adjust to response.
Polyarticular-course Juvenile Rheumatoid Arthritis (PJIA)	Start 10 mg/m ² once weekly and adjust to response. For doses 20 to 30 mg/m ² /week (0.65 to 1.0 mg/kg/week), IM or SC dosing may be better tolerated.

Source: Hospira Methotrexate Prescribing Information

The experience with methotrexate over all the approved indications covers a much wider range of doses than those associated with RA or psoriasis, which by convention does not typically exceed 30 mg/week.^{13, 14} The toxicity of methotrexate is well known, based on the high doses of it used to treat neoplastic diseases—an order of magnitude higher (i.e. 20 to 30 grams) for the treatment of osteosarcoma, which approximates the maximum tolerated dose, and requires leucovorin rescue. Subcutaneous administration of methotrexate for RA and psoriasis involves doses at the low end of the methotrexate therapeutic range, and a 33-66% higher exposure with the Rasuvo methotrexate autoinjector (study MC-MTX.14/PK) would not be expected to result in significant additional toxicities.

Although the most common toxicities observed with methotrexate are gastrointestinal toxicities such as nausea, stomatitis, and gastrointestinal upset, concerns were raised about the potential for long-term hepatotoxicity due to the observation of elevated liver enzymes, particularly in the psoriasis experience of the 1960's. This led to a multiple-decades' practice of regular liver enzyme tests and intermittent liver biopsies. Liver biopsies fell out of favor in rheumatology practice as it became evident that liver damage was not likely, even with long-term methotrexate use (e.g. 10 years).¹⁵ For patients with psoriasis, updated guidelines regarding the use of liver biopsy have been published. Generally, liver biopsy is only recommended in patients with risk factors for hepatotoxicity.¹⁶ Other potential serious toxicities with methotrexate include myelosuppression and pulmonary toxicity (i.e. pneumonitis). Renal impairment increases the risk of methotrexate toxicity, particularly myelosuppression.

¹² Average height and weight of US adult: <http://www.cdc.gov/nchs/fastats/bodymeas.htm>

¹³ Visser, et al. *Ann Rheum Dis* 2009; 68:1086-1093.

¹⁴ Kuijpers ALA, van de Kerhof. *Am J Clin Dermatol* 2000;1:27-39.

¹⁵ Kremer JM. *J Rheum* 1996; 44:34-37

¹⁶ Menter A, et al. *J Am Acad Dermatol* 2009;61:451-85.

Based on these concerns, it is standard practice to get baseline liver enzymes, creatinine, complete blood count, and chest x-ray and to screen patients for risk factors such as regular alcohol intake. In addition, 5 mg of folic acid per week is given to reduce the incidence of GI toxicity and bone marrow suppression. Regular monitoring of liver enzymes, creatinine, and blood count is performed for the duration of therapy.¹³

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

The safety experience specific to the Rasuvo methotrexate autoinjector product is limited to three single or 2-dose studies:

- Study MC-MTX.14/PK, an open-label, 2-way, single dose crossover bioavailability study in healthy volunteers comparing methotrexate exposure following SC administration with the Rasuvo methotrexate autoinjector into the abdomen with the same dose of approved methotrexate tablets administered orally. Subjects were randomized to receive 7.5, 15, 22.5, or 30mg of methotrexate SC or orally followed by a second dose by the alternate route two weeks later. This study enrolled 65 healthy male and female subjects 18-55 years of age. There were no SAEs or deaths during the study. Three subjects discontinued the study due to an AE: one because the event made continuation of the study undesirable, and two because the AEs fulfilled the withdrawal criteria. Approximately half (56.5%) of subjects reported an AE during the study. Most were mild in intensity. Gastrointestinal AEs were more frequently reported by subjects after oral dosing than after SC dosing.
- Study MC-MTX.15/HF, was an open-label, two dose, actual use and PK study in patients with RA that evaluated patient's ability to use the Rasuvo autoinjector device and its instructions, after having received training in the use of this product. Patients received two doses of methotrexate 15mg SC administered with the Rasuvo autoinjector. This study included 106 RA patients ≥ 16 years who were on methotrexate treatment or were candidates for methotrexate treatment. There were no SAEs. Three AEs were reported: 1 diarrhea, 1 toothache, and 1 upper respiratory tract infection.
- Study MC-MTX.12/PK, a single dose, 2-period, 2-treatment, open-label, randomized crossover study evaluating the relative bioavailability of 30mg of methotrexate administered SC with the Rasuvo methotrexate autoinjector with the same dose of methotrexate administered IM using the Hospira injectable product. The study enrolled 35 patients with moderate to severe psoriasis ages 18 to 65 years who were either on methotrexate or were eligible for methotrexate treatment. Eligible patients were randomly assigned to receive each of the treatments (Hospira methotrexate IM and Rasuvo methotrexate SC). A washout period of 7 days separated the treatments. There were no deaths, SAEs, or AEs leading to discontinuation. Following IM administration, 8 patients (24%) reported an AE. Two patients (6%) reported moderate

AEs of headache and one patient (3%) reported a severe AE of headache. Following SC administration, 14 patients (41%) reported an AE. Five patients (15%) reported moderate AEs (2 headache, 1 limb injury, 1 wound, 1 contact dermatitis, and 1 urticaria).

Based on these limited data, no new safety signals were identified.

- **Immunogenicity**

Immunogenicity was not assessed. As a small molecule chemical, methotrexate has not been, nor would it be expected to be, associated with significant immunogenicity.

- **Special safety concerns**

Device usability studies

One use and handling study was performed to evaluate the ability of patients to follow the instruction set and use the device (MC-MTX.15/HF). This study is intended to support the conclusion that the device can be used safely if approved, but is not informative to prescribers and will not be described in labeling.

Study MC-MTX.15/HF was a multicenter, open-label, two dose, actual use and PK study in patients with RA that evaluated patient's ability to use the Rasuvo autoinjector device and its instructions, after having received training in the use of this product. At Visit 1 (Day 1), the training consisted of a description of the proper technique for using the autoinjector using the Patient Instructions for Use (IFU). Training was provided in the physician's office by a healthcare professional. After training, the patient was asked to perform a self-injection with the healthcare professional available to answer questions and provide assistance if needed. The healthcare professional completed a questionnaire related to the patient's label comprehension.

At Visit 2 (Day 8 to 10), patients were tested via a written examination followed by human factors observation of the patient performing a self-injection without provision of assistance or training from the healthcare professional. On the written examination, a passing score was 80%, i.e., 8 correct answers out of the 10 questions, although the study report also notes that a single re-test was permitted without specifying how this would be performed.

Almost all patients (98% of 106 patients) were able to pass the written exam (80% correct), and perform a successful SC injection of study drug. A total of 210 injections were documented over the course of the study. Upon inspection, all pens (210/210) were found to be intact after use. After all of the injections the protective needle shield was noted to have completely moved back into place, completely covering the needle. Along with an additional simulated use study in which the needle shield activated automatically in all (390/390) cases, this satisfies the Agency's concerns that the sharps protection feature incorporated into the device be adequately tested (see the CDRH Guidance for Sharps Injury Protection features at: <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/Guidanc>

eDocuments/ucm071755.pdf).

There were two descriptions of device related issues. First, one pen was reported to have a “slight bend” in the needle after injection. However, the needle was not broken and the pen was otherwise intact. In addition, the injection was successful as the full dose was administered with no fluid left in the product. Second, fluid was noted to be deposited in the wall of the control shield of a second pen. In response to an information request, the Applicant explained that this was due to a patient having prematurely lifted the pen from the skin rather than due to a device failure.

Six patients did not adequately complete an injection: four at the first visit and two at the second visit. At the first visit, the incomplete injections were secondary to lifting the pen too early. At the second visit, the incomplete injections were secondary to nervousness and not used to an injection. The study report notes these as potential device malfunctions, but the Applicant noted that these were reclassified as being related to human factors issues. No significant safety concerns were observed. The Division of Medication Error Prevention and Analysis (DMEPA, Teresa McMillan), the Center for Devices and Radiological Health Human Factors (CDRH, QuynhNhu Nguyen), and Dr. Starke reviewed the study results and noted that while there were limitations, it appeared to support that RA patients could use the device.

The Applicant argues that the incomplete injections can be addressed by adequate training and I agree.

- **Safety conclusions**

Dr. Starke and Dr. Cook have concluded that there is adequate evidence to support the safety of methotrexate administered subcutaneously for RA and psoriasis, and I concur. While incomplete injections occurred in the study, it is important to consider the context of evaluating the acceptability of the device. Specifically, methotrexate will not be administered under emergency conditions, thus use of the device does not have to be immediately intuitive. In addition, methotrexate is a chronically administered drug. Although some errors may occur when users are unfamiliar with the device, this would be likely with any device, and the potential concerns raised by the incomplete injections in the actual use study will not be an issue when patients/providers become familiar with use. Incomplete injections were more likely to result in lack of medication administration, or partial medication administration. Because methotrexate is not an emergency medication, and is not a narrow therapeutic index product, lack of, or partial, administration would not be expected to result in clinically significant concerns. Lastly, the device is acceptable from the standpoint of the reviewers from the Center for Devices and Radiological Health and conforms to CDRH standards for similar devices.

Based on these considerations, I am of the opinion that there are no safety concerns with the device that would preclude approval.

- **Discussion of notable safety issues (resolved or outstanding)**

See above.

9. Advisory Committee Meeting

An advisory committee meeting was not held for this application. Methotrexate is an approved drug and no issues were identified that would warrant advisory committee input.

10. Pediatrics

The following section is largely excerpted from Dr. Starke's clinical review:

Methotrexate is currently approved for the indication of treatment of rheumatoid arthritis when administered by **oral** route; for the indication of "polyarticular-course juvenile rheumatoid arthritis" (now termed polyarticular juvenile idiopathic arthritis, or PJIA), when administered by **oral**, **IM** or **IV** routes. The application therefore triggers the Pediatric Research Equity Act (PREA, 21 U.S.C. 355c) for the indication of RA and severe psoriasis, for which this is a new route of administration. The addition of an auto-injector to an injectable methotrexate, making this a drug/device combination, does not trigger PREA as this change is not considered to be a new dosage form.

Approvals in RA have triggered pediatric study requirements in PJIA under PREA. Studies in PJIA patients under 2 years of age have been typically waived due to the rarity of the diagnosis in children under 2 years, which would make studies infeasible. The Applicant has asked for a waiver for children ≤ 2 years because the necessary studies are impossible or highly impractical as the number of patients with JIA is not substantial. This is acceptable and consistent with what the Division has done for other applications with these indications. For children greater than 2 years of age, the PREA requirements are satisfied by the Agency's previous findings of safety and effectiveness of methotrexate for JIA.

With regard to the psoriasis indications, the Applicant has asked for a waiver in children 0 to 17 years because of safety concerns with use in this population. Methotrexate has the potential for serious toxic reactions (which can be fatal), and the labeling carries a BOXED WARNING for multiple safety concerns. Additionally, as currently worded in the labeling, periodic liver biopsy is recommended during the treatment of patients with psoriasis. As a result, the Applicant argues that safety concerns posed by the drug outweigh the potential benefits of treatment in pediatric psoriasis. DDDP agrees with granting of a waiver of studies in the pediatric population with psoriasis for safety reasons, and will label the product accordingly. This is consistent with the current labeling and what has been done for other applications.

Both Divisions discussed their recommendations with the Pediatric Review Committee (PeRC) on April 2, 2014, and PeRC concurred with the recommendations stated above. However, PeRC did recommend that the language in Section 8.4 reflect the safety concerns that underlie the risk/benefit decision with regard to not labeling for use in children with psoriasis. The Division considered the recommendation from PeRC and concluded that the statement in the labeling concerning the pediatric population is sufficient.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not applicable
- **Exclusivity or patent issues of concern**

The Applicant submitted the required patent certification with respect to the listed drugs.

(b) (4)

- **Financial disclosures**—No issues.
- **Other GCP issues**—No issues
- **DSI audits**—

The Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and analytical portions of study MC-MTX.14/PK. For the inspection of the clinical portion, there were no objectionable findings during the inspection and Form FDA-483 was not issued. For the inspection of the analytical portion, there were no objectionable findings during the inspection and Form FDA-483 was not issued. The results from the clinical and bioanalytical portions of study MC-MTX.14/PK were felt to be acceptable for Agency review.

- **Any other outstanding regulatory issues**—Not applicable.

12. Labeling

- **Proprietary name**—the initially proposed proprietary name, (b) (4) was found to be not acceptable. On December 20, 2013, the Applicant proposed the proprietary name Rasuvo, which was reviewed and determined to be acceptable.
- **Physician labeling**

The Rasuvo autoinjector is essentially a parenteral methotrexate formulation, like the currently approved parenteral methotrexate formulations, only packaged for subcutaneous injection. The parenteral methotrexate formulations are also labeled for subcutaneous use (albeit only directly mentioned for the polyarticular course juvenile idiopathic arthritis indication). The labeling for the Rasuvo autoinjector is the second instance of Prescribing Information (PI) in Physicians Labeling Rule (PLR) format for a methotrexate product. A different methotrexate autoinjector, Otrexup (NDA 204824) was approved on October 11, 2013, approximately one month after submission of this application. In determining the most appropriate approach for the Otrexup methotrexate label, multiple internal meetings with other Agency stakeholders in this process, including the Division of Oncology Products 2 (the home division for the methotrexate products), the Study Endpoints and Labeling Development team (SEALD), and the Division of Dermatology and Dental Products (DDDP). The Office of Drug Evaluation 2 Director Dr. Curtis Rosebraugh and Office of New Drugs Director Dr. John Jenkins were also briefed and provided feedback on the most appropriate approach. For Otrexup, the group agreed that it is difficult to justify labeling this product very differently from other parenteral methotrexate products. See Dr. Yim's Division Director Review memo dated October 11, 2013 for additional details.

Similar considerations occurred for the current labeling situation for the Rasuvo autoinjector. It was felt that it was difficult to justify labeling it very differently from other parenteral methotrexate products. The Applicant's primary data to support approval of their product was relative bioavailability data to approved oral methotrexate. The bulk of the efficacy and safety information in the Rasuvo NDA was from published literature on methotrexate and the Agency's previous finding of efficacy and safety of oral and parenteral methotrexate, and was not specific to the Rasuvo methotrexate product. Therefore the bulk of the information that would be utilized to update the label would be based on publically available information not owned by Medac, would be applicable to all parenteral methotrexate products, and should be in all parenteral methotrexate labels. Additionally, the proposed Rasuvo label submitted by the Applicant was not a comprehensive update of the parenteral methotrexate label, and would not have been sufficient to serve as a model for PLR conversion of the approved parenteral methotrexate labels. Thus, the review team felt that a PLR label with fully updated content would require much additional effort and would not be possible within the timeframe of the Rasuvo NDA cycle.

Therefore, the group determined the most appropriate path forward was to utilize a non-product specific methotrexate PLR label based on information in the listed reference products labels converted into PLR format. Since Otrexup and Rasuvo referenced the same listed

drugs, the PIs for both labels are similar and retain much of the language that is in the reference labels, except with regard to any information that is product-specific. The primary difference between the Rasuvo label and the listed drugs' labels is the addition of BA/BE results for Rasuvo in Section 12.3 Pharmacokinetics and information in Section 2 Dosage and Administration advising prescribers to consider the differences in bioavailability between oral and subcutaneously administered methotrexate. Additionally, the neoplastic disease indications were removed from the indications and usage section, as Rasuvo is not designed to accommodate the doses and routes of administration currently approved for methotrexate in the neoplastic disease setting. However, unless a given toxicity was clearly only applicable to the neoplastic disease setting, safety information remained in the label, even if likely derived from cancer studies.

A future update of the content of all parenteral methotrexate labels will be accomplished via PLR conversion of the listed drug (NDA 11719 Hospira) with a contemporaneous labeling supplement request for an update of the Rasuvo methotrexate label, once the updated content for the parenteral methotrexate labels is agreed up.

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review.**

See above. Labeling negotiations are ongoing with the Applicant at the time of this review.

- **Carton and immediate container labels**

Revisions were recommended by DMEPA and negotiations are ongoing at the time of this review.

- **Patient labeling/Medication guide**

Revisions for patient information sheet and instructions for use were recommended by DMEPA and Division of Medical Policy Programs patient labeling team. Negotiations are ongoing at the time of this review. Methotrexate does not have a medication guide.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of this application, provided that agreement can be reached on revisions to the proposed labeling and pending satisfactory inspectional findings.

- **Risk Benefit Assessment**

The risk-benefit of the SC route of administration of methotrexate is favorable for RA and severe psoriasis. This is based on a modest increase in exposure with SC administration

relative to oral administration that allows for extrapolation of the efficacy of oral methotrexate for RA and severe psoriasis. The safety of SC administration for RA and severe psoriasis is also based on the modest increase in exposure with SC administration relative to the conventionally used doses for RA and psoriasis, which are on the low end of the approved therapeutic dose range of methotrexate. The increase in exposure associated with SC administration would not be expected to have a clinically significant impact on the safety profile of methotrexate in RA or severe psoriasis.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

Postmarketing risk evaluation and management strategies are not warranted on the basis of this submission.

- **Recommendation for other Postmarketing Requirements and Commitments**

Postmarketing requirements and commitments are not warranted on the basis of this submission.

- **Recommended Comments to Applicant**

Not applicable.

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/s/

JANET W MAYNARD
06/19/2014